The 2-aminotetralin system as a structural base for new dopamine- and melatonin-receptor agents

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RIJKSUNIVERSITEIT GRONINGEN

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PROEFSCHRIFT

ter verkrijging van het doctoraat in de
Wiskunde en Natuurwetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus Dr. F. van der Woude
in het openbaar te verdedigen op
vrijdag 21 oktober 1994
des namiddags te 4.00 uur

door

Swier Copinga

geboren op 24 januari 1965
te Groningen

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The studies described in the second part of this thesis were financially supported by Glaxo Group Research Ltd. (Ware, Hertfordshire, UK).

Cover

Cor and Eric Grol - The "genesis" of the molecular structures of 5,6-dihydroxy-2-[N-*n*-propyl-N-2-(2-thienyl)-ethylamino]tetralin [5,6-$(OH)_2$-PTAT] and 8-methoxy-2-(acetamido)tetralin [8-MeO-AAT].

Printing

Krips Repro, Meppel, The Netherlands

It is but sorrow
to be wise
when wisdom profits not

Sophocles (496 BC - 405 BC)
Oedipus the King

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PREFACE

The research described in this thesis can be divided into two parts as a consequence of the tragic death of Prof. Dr. A.S. Horn on January 2, 1990. The first part belongs to a research project aiming at the development of 2-aminotetralins and related compounds as dopamine-receptor agents. The second part belongs to another research project directed to the development of 2-amidotetralins and related compounds as nonindolic melatonin-receptor agents. Both research projects are representative of the research performed at the Department of Medicinal Chemistry, University Centre for Pharmacy, Groningen, presently led by Prof. Dr. H.V. Wikström. The second research project is performed in collaboration with the Department of Pharmacology (Prof. Dr. M.L. Dubocovich), Northwestern University Medical School, Chicago (USA), and Glaxo Group Research Ltd., Ware (UK).

SCOPE OF THE THESIS

Based on the hypothesis developed in the 1980's that stimulation of both dopamine D_1 and D_2 receptors would be needed for a good clinical result in the early stages of Parkinson's disease, the aim of the first part of this thesis was to develop a novel 2-aminotetralin as a mixed D_1/D_2-receptor agonist. Ultimately, such an agent could be used clinically in conditions where stimulation of D_1 receptors as well as D_2 receptors is needed. Chapters 1 to 3 constitute this part of the thesis. Chapter 1 provides a general introduction on central dopamine neurotransmission, dopamine receptors, dopamine-receptor agents, and dopamine-receptor interactions. Chapters 2 and 3 describe the synthesis and the pharmacological evaluation of 5,6-dihydroxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]tetralin [5,6-$(OH)_2$-PTAT] as a mixed D_1/D_2-receptor agonist. In addition, these chapters describe the development of 5,6-methylenedioxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]tetralin [5,6-OCH_2O-PTAT] as a potential prodrug of 5,6-$(OH)_2$-PTAT.

Based on the successful development of 2-aminotetralins as serotonin-receptor agents, and taking into account the similarities and differences between the chemical structures of the neurotransmitter serotonin and the hormone melatonin, the aim of the second part of this thesis was to develop 2-amidotetralins as nonindolic melatonin-receptor agents. These agents could play an important role in the characterization of melatonin receptors as well as in the elucidation of the mode of action of melatonin. Chapters 4 to 6 make up this part of the thesis. Chapter 4 merely reviews the current status of melatonin research. Chapter 5 deals with the synthesis and pharmacological evaluation of 8-methoxy-2-amidotetralins and related compounds as melatonin-receptor agonists. Chapter 6 describes the synthesis and pharmacological evaluation of 4-benzyl- and 4-phenyl-2-amidotetralins as melatonin-receptor agonists and antagonists, respectively.

In the general discussion the use of the 2-aminotetralin system as a structural base for the development of conformationally restricted analogues of different kinds of biologically active substances, such as dopamine and melatonin, is evaluated.